Usefulness of Serum N-Terminal Pro–Brain Natriuretic Peptide to Predict In-Stent Restenosis in Patients With Preserved Left Ventricular Function and Normal Troponin I Levels

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The level of N-terminal pro–B-type natriuretic peptide (NT–pro-BNP) is a strong predictor of mortality in patients with acute coronary syndrome and may be a strong prognostic marker in patients with chronic coronary artery disease. We investigated whether NT–pro-BNP could predict in-stent restenosis (ISR) in asymptomatic patients with preserved left ventricular (LV) systolic function who underwent percutaneous coronary intervention. We measured serum NT–pro-BNP levels in 249 patients (61 ± 9 years of age; 73% men) with preserved LV systolic function (ejection fraction >50%) who underwent follow-up coronary angiography. Initial diagnoses were stable angina in 50 (20%), unstable angina in 133 (53%), and myocardial infarction in 66 (27%). Baseline characteristics between groups with ISR (n = 92) and without ISR (n = 157) were similar. The level of NT–pro-BNP was higher in patients with ISR than in those without ISR (222 ± 327 vs 94 ± 136 pg/ml, p = 0.001). In the ISR group, NT–pro-BNP level was higher in patients with left anterior descending coronary artery ISR (n = 53, 312 ± 479 pg/ml) than in those with left circumflex coronary artery ISR (n = 19, 115 ± 98 pg/ml, p = 0.018). At the standard cutoff of >200 pg/ml, a high NT–pro-BNP level indicated a high probability of ISR (odds ratio 2.18, 95% confidence interval 1.0 to 4.5, p = 0.038). In multivariate analysis, NT–pro-BNP level was an independent predictor for ISR. In conclusion, NT–pro-BNP could be a predictor of ISR in asymptomatic patients with preserved LV systolic function. **(Am J Cardiol 2007;99:1051–1054)**

With the introduction of drug-eluting stents, in-stent restenosis (ISR) has markedly decreased. However, ISR remains problematic in complex lesions and diabetes mellitus. Brain (B-type) natriuretic peptide (BNP) is a neurohormone synthesized and released from cardiac ventricles in response to increased wall tension.[1] BNP level is increased in patients with heart failure, and this level increases in proportion to the degree of left ventricular (LV) dysfunction. BNP level also increases after myocardial infarction (MI) and in unstable angina pectoris. BNP is produced as a prohormone, pro-BNP, which is enzymatically cleaved into BNP and the amino-terminal portion of the prohormone, N-terminal pro-BNP (NT–pro-BNP). The present study determined whether serum NT–pro-BNP levels could predict ISR.

Methods and Results

Two hundred forty-nine asymptomatic patients (61 ± 9 years of age; 73% men) with preserved LV systolic function (ejection fraction >50%) who underwent follow-up coronary angiography were enrolled. We prospectively analyzed patients admitted to the Department of Cardiology of Chonnam National University Hospital (Gwangju, South Korea) from November 2003 to June 2005 who were eligible for participation in this study.

All patients underwent echocardiography before follow-up coronary angiography. The main inclusion criteria were preserved LV systolic function, normal troponin I level (≤0.05 ng/ml), normal C-reactive protein (CRP), myoglobin, other cardiac enzymes, and normal creatinine clearance rate. The main exclusion criteria were Canadian Cardiology Society angina class >II, LV ejection fraction ≤50 % on echocardiogram, troponin I level >0.05 ng/ml, myoglobin level >92.5 ng/ml, creatine kinase-MB level >9.5 U/L, CRP level >0.5 mg/dl, and calculated creatinine clearance rate <80 ml/min/m^2. All clinical data were collected prospectively.

Peripheral blood samples for serum NT–pro-BNP were obtained before follow-up coronary angiography by direct venipuncture of the antecubital vein after a patient had been resting in the supine position for 30 minutes. Blood samples were collected in tubes without anticoagulant. Samples were then centrifuged, and serum was stored frozen in aliquots at −70°C within 30 minutes. Serum NT–pro-BNP level was measured by an electrochemiluminescence "sandwich" immunoassay method for NT–pro-BNP using an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany). This electrochemiluminescence sandwich immu-

The Heart Center of Chonnam National University Hospital, Gwangju, South Korea. Manuscript received August 12, 2006; revised manuscript received and accepted November 27, 2006.

This study was supported in part by the Cardiovascular Research Foundation, Seoul, Korea.

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0002-9149/07/$ – see front matter
doi:10.1016/j.amjcard.2006.11.069

Table 1
Baseline characteristics

Variable	ISR (n = 92)	No ISR (n = 157)	p Value
Age (yrs)	62 ± 8	61 ± 9	0.230
Men	65 (71%)	116 (73%)	0.580
Hypertension	47 (51%)	87 (55%)	0.509
Diabetes	32 (35%)	38 (24%)	0.073
Smoking	25 (27%)	35 (22%)	0.385
Dyslipidemia	36 (42%)	58 (38%)	0.630
Ejection fraction (%)	67 ± 8	69 ± 7	0.062
Creatinine (mg/dl)	1.0 ± 0.2	1.0 ± 0.2	0.093
CRP (mg/dl)	0.2 ± 0.4	0.2 ± 0.5	0.721
Troponin I (ng/ml)	0.04 ± 0.01	0.04 ± 0.01	0.421
CK-MB (U/L)	4.2 ± 2.9	4.4 ± 3.1	0.700
Homocysteine (μmol/L)	9.0 ± 2.9	8.8 ± 3.4	0.747
Fibrinogen (mg/dl)	248 ± 88	229 ± 88	0.196
LDL cholesterol (mg/dl)	98 ± 33	96 ± 38	0.669
Lipoprotein(a) (mg/dl)	34 ± 27	26 ± 35	0.067
History			0.616
Stable angina	16 (17%)	34 (22%)	
Unstable angina	49 (53%)	84 (54%)	
MI	27 (29%)	39 (25%)	
Target coronary artery			0.495
Left anterior descending	53 (58%)	101 (64%)	
Left circumflex	19 (21%)	28 (18%)	
Right	20 (22%)	28 (18%)	
Complex lesions (B2 or C)	49 (53%)	83 (53%)	0.948
Stent diameter (mm)	3.2 ± 0.3	3.2 ± 0.2	0.939
Stent length (mm)	27.7 ± 3.5	27.4 ± 1.8	0.468
Drugs			
Angiotensin-converting enzyme inhibitors	32 (35%)	29 (19%)	0.061
Angiotensin II type I receptor blockers	45 (49%)	94 (60%)	0.246
β blockers	66 (72%)	98 (62%)	0.313
Calcium antagonists	24 (26%)	56 (36%)	0.262
Statins	77 (84%)	143 (91%)	0.212

CK-MB = creatine kinase-MB; LDL = low-density lipoprotein.

noassay detects photons using polyclonal antibodies (a biotinylated antibody and a ruthenium derivative-labeled antibody) in a 2-V electric field. It has high sensitivity and specificity and a large detection range. The analytic range of NT–pro-BNP assay is 5 to 35,000 ng/L. The reference value changes according to age and gender. In our institute, reference values are <88 pg/ml in men and <153 pg/ml in women.

Troponin-I levels were also measured by electrochemiluminescence sandwich immunoassay before follow-up coronary angiography in all patients.

All patients underwent coronary angiography according to a common technique. Angiograms were analyzed with a validated quantitative coronary angiographic system (Philips H5000, Philips Medical Systems, Andover, Massachusetts; Allula DCI program, Philips Medical System, Best, The Netherlands). Images with optimum delineation of the target lesion were selected from among all technically suitable angiograms, and quantitative coronary angiography was performed by 2 physicians without any knowledge of patients' clinical history and levels of NT–pro-BNP.

All metric variables were presented as mean ± SD. Differences in metric variables between groups were analyzed using Student's *t* test. Correlations between NT–pro-BNP and parameters were described by Pearson's correlation. Prediction power of NT–pro-BNP for coronary artery lesions was calculated with multivariate logistic regression analysis. All statistical processes were performed using SPSS 11.0 (SPSS, Inc., Chicago, Illinois). A p value <0.05 was considered statistically significant.

Table 2
Procedural results

Variable	ISR (n = 92)	No ISR (n = 157)	p Value
Reference vessel diameter (mm)	3.3 ± 0.3	3.3 ± 0.4	0.978
Lesion length (mm)	27.1 ± 6.3	27.0 ± 5.5	0.549
Peak deployment pressure (atm)	13 ± 2	13 ± 2	0.533
TIMI grade 3 flow	90 (98%)	157 (100%)	0.069
Minimal lumen diameter (mm)			
Before procedure	0.9 ± 0.6	0.9 ± 0.7	0.713
After procedure	2.3 ± 0.5	2.3 ± 0.6	0.791
Follow-up	1.3 ± 1.1	2.1 ± 0.6	<0.001
Diameter stenosis (%)			
Before procedure	69 ± 16	68 ± 18	0.749
After procedure	9 ± 7	8 ± 7	0.565
Follow-up	52 ± 18	23 ± 12	<0.001
Acute gain (mm)	1.4 ± 0.7	1.4 ± 0.6	0.898
Late loss (mm)	1.0 ± 1.1	0.2 ± 0.5	<0.001
Type of stent: drug-eluting stent	15 (16%)	60 (38%)	0.019

TIMI = Thrombolysis In Myocardial Infarction.

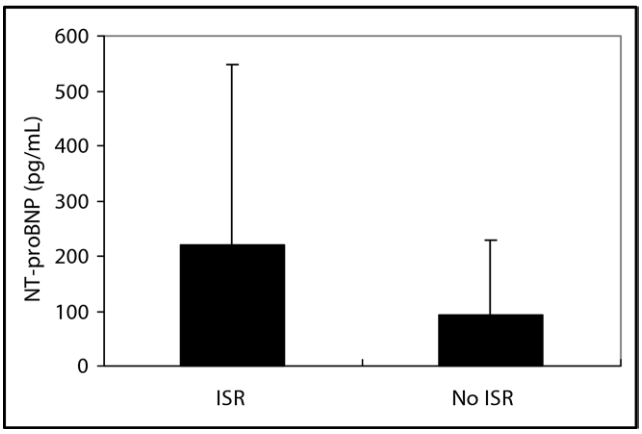

Figure 1. NT–pro-BNP level in patients with and without ISR (p = 0.001). Values are means ± SDs (n = 92 in ISR group, n = 157 in no-ISR group).

Detailed baseline characteristics of patients who subsequently developed asymptomatic restenosis (n = 92) compared with those who did not (n = 157) are listed in Table 1. No significant differences in age, gender, coronary risk factors, global LV systolic function, renal function, biochemical markers, including cardiac enzymes, lipid profiles, initial clinical diagnosis, and target coronary arteries, were observed between groups.

Table 2 presents summary data for quantitative angiographic findings. No significant differences were recognized in target lesions, reference lumen diameter, minimum luminal diameter, and percent diameter stenosis immediately after stenting.

Levels of NT–pro-BNP were 222 ± 327 pg/ml in the ISR group and 94 ± 136 pg/ml in the no-ISR group (p =

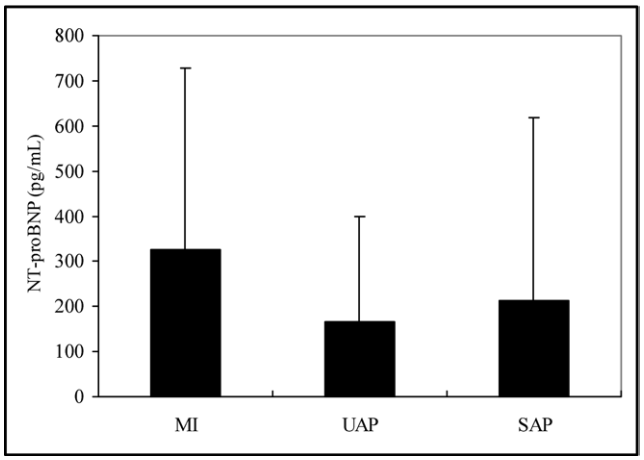

Figure 2. Association between NT–pro-BNP level and initial diagnosis in ISR group. Values are means ± SDs (n = 16 patients with stable angina pectoris [SAP], n = 49 patients with unstable angina pectoris [UAP], n = 27 patients with MI).

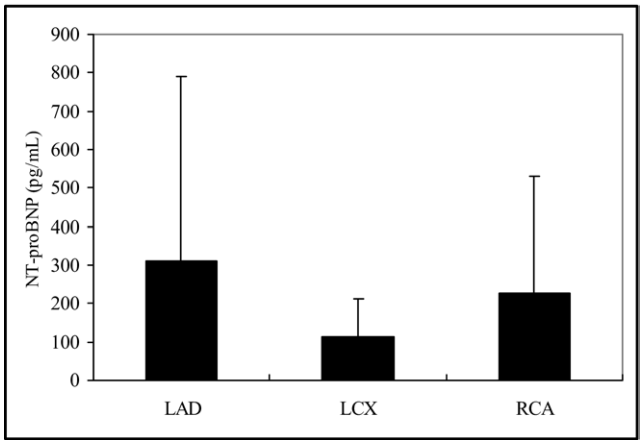

Figure 3. Association between NT–pro-BNP level and target coronary artery in ISR group. Values are means ± SDs (n = 53 in the left anterior descending coronary artery [LAD], n = 19 in the left circumflex coronary artery [LCX], n = 20 in the right coronary artery [RCA]; LAD vs LCX, p = 0.018).

Table 3
Correlation between N-terminal pro–B-type natriuretic peptide level and multiple variables

Variable	Correlation (r)	p Value
Age	0.176	0.015
Ejection fraction	−0.182	0.008
Troponin I	0.062	0.333
CRP	−0.003	0.975
Homocysteine	0.146	0.027
Fibrinogen	0.044	0.570
LDL cholesterol	−0.057	0.384
Lipoprotein(a)	0.120	0.116

Abbreviation as in Table 1.

0.001) (Figure 1). In the ISR group, no difference in the level of NT–pro-BNP was observed according to the initial diagnosis (Figure 2). In the ISR group, the level of NT–pro-BNP was significantly higher in the left anterior descending coronary artery target lesion than in the left circumflex artery target lesion (p = 0.018; Figure 3).

Table 4
Independent predictive factors for in-stent restenosis

Variable	Odds Ratio	95% CI	p Value
Age	1.181	0.643–2.168	0.592
Hypertension	0.635	0.355–1.136	0.126
Diabetes	1.771	0.939–3.340	0.078
Smoking	1.368	0.696–2.687	0.364
Dyslipidemia	1.122	0.623–2.020	0.702
CRP	1.289	0.331–5.025	0.714
Fibrinogen	1.518	0.570–4.040	0.404
Drug-eluting stent	4.627	1.945–11.008	0.011
NT–pro-BNP (>200 pg/ml)	2.180	1.046–4.542	0.038

CI = confidence interval.

The level of NT–pro-BNP was positively correlated with age and homocysteine level and negatively correlated with ejection fraction (r = 0.176, p = 0.015; r = 0.146, p = 0.027; r = −0.182, p = 0.008; Table 3).

Multivariate logistic regression analyses of the association between coronary artery stenosis and multiple parameters are presented in Table 4. In multivariate analysis, NT–pro-BNP was a predictor of ISR independent of age, gender, ejection fraction, antecedent hypertension or diabetes, creatinine, total cholesterol, and other inflammatory markers in these patients. The most powerful parameter to predict ISR was NT–pro-BNP (odds ratio 2.18, 95% confidence interval 1.0 to 4.5, p = 0.038; Table 4).

Discussion

In this study, the level of NT–pro-BNP was higher in patients with ISR than in those without ISR who had coronary artery disease with normal LV systolic function and normal troponin I level. In addition, the level of NT–pro-BNP was significantly higher in patients with ISR after drug-eluting stent implantation than in those without ISR (data not shown). Nishikimi and Matsuoka[2] measured atrial natriuretic peptide, N-terminal pro–atrial natriuretic peptide, and BNP before and 3 to 6 months after percutaneous coronary intervention (PCI) in patients with MI of recent onset and reported that plasma levels of atrial natriuretic peptide, N-terminal pro–atrial natriuretic peptide, and BNP significantly decreased in patients without restenosis, but these natriuretic peptide levels did not change after PCI in patients with restenosis. Unfortunately, we did not evaluate baseline level and serial changes in NT–pro-BNP. Because of differences in initial diagnoses in this study group, it is impossible to evaluate the relation between baseline level of NT–pro-BNP and ISR.

However, the Fragmin and Fast Revascularisation During In Stability in Coronary Artery Disease (FRISC)[3] II substudy showed that the initial increase in NT–pro-BNP in non–ST-segment elevation acute coronary syndrome is mainly reversible and that, after the early rapid decrease, NT–pro-BNP levels continue to decrease for ≥6 months. Kalra et al[4] reported that, in patients with increased levels of NT–pro-BNP at baseline, PCI was associated with a de-

crease in concentrations within 24 hours, and this decrease was maintained at 6 months and was associated with improved LV function or a decreased ischemic burden. The population of this study was asymptomatic and had preserved LV systolic function after undergoing stent implantation with complete revascularization. No significant residual stenosis was observed on coronary angiography just after stent implantation.

In the present study, patients with left anterior descending coronary involvement had the highest NT–pro-BNP levels. No significant differences were observed in target coronary arteries with respect to the variables of age, gender, coronary risk factors, LV ejection fraction, and initial diagnosis. We previously reported that plasma level of NT–pro-BNP is a sensitive marker of myocardial ischemia and correlates with extent of coronary artery disease.[5] We suggest that the difference was caused by difference in ischemic burden between each coronary artery.[5]

This study has limitations. Our study population included patients with previous MI. An increased NT–pro-BNP level is related to LV remodeling after MI.[6,7] We excluded patients with subsequent LV remodeling after MI. Recent studies have shown that levels of NT–pro-BNP are higher in patients with increased LV filling pressure in the presence of normal LV systolic function.[8,9] Diastolic function was not evaluated in this study. Because systolic dysfunction is preceded by diastolic dysfunction during the course of heart failure, it would be valuable to investigate the relation between NT–pro-BNP and diastolic function.

This study population was asymptomatic and had normal troponin I level, normal CRP level, normal renal function, and preserved LV systolic function. In these situations, it is very difficult to predict ISR before coronary angiography. However, we predict >50% coronary artery stenosis when NT–pro-BNP was >200 pg/ml. The present results suggest that NT–pro-BNP would be a useful screening test for ISR in patients with coronary artery disease, normal troponin I level, and preserved LV systolic function.

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